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(54) **Pharmaceutical multiple-units formulation.**

(57) A pharmaceutical oral controlled release multiple-units formulation in which individual units comprise cross-sectionally substantially homogeneous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating which is substantially resistant to gastric conditions, but which is erodable under the conditions prevailing in the small intestine, in particular an enteric coating which is substantially insoluble at a pH below 7 such as Eudragit® S (an anionic polymerisate of methacrylic acid and methacrylic acid methyl ester), is prepared by a process comprising comminuting an active substance together with a substance which is readily soluble in intestinal fluids such as an anionic detergent to obtain particles containing the active substance in intimate admixture with the readily soluble substance, combining the resulting particles into cross-sectionally substantially homogeneous cores together with components which accelerate the disintegration of the cores in intestinal fluids such as talc and sucrose, coating the individual cores with the coating, and combining a multiplicity of the coated cores into a capsule or tablet formulation.

As the coating is erodable in an alkaline environment only, the active substance is not released until the units arrive at a section of the small intestine with an alkaline pH. Thus, a reduction and delay of the peak plasma concentration is obtained without affecting the extent of drug availability.

A coating of the above-defined type may also be used when the active substance is a substance which exerts an irritating effect on the gastric mucosa and/or is unstable in an acidic environment.

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PHARMACEUTICAL MULTIPLE-UNITS FORMULATION

The present invention relates to oral pharmaceutical controlled release multiple-units dosage forms with important new features.

TECHNICAL BACKGROUND

Many physiological factors influence both the gastrointestinal transit time and the release of a drug from a controlled release dosage form and thus the uptake of the drug into the systemic circulation. Dosage forms should therefore be designed so that such variable factors do not compromise the efficacy and safety of the product.

In humans, a reproducible gastrointestinal transit time of a depot formulation can be achieved only by a controlled release multiple-units dosage form.

The term "controlled release multiple-units formulation" (Bechgaard & Hegermann Nielsen, 1978) indicates a pharmaceutical formulation comprising a multiplicity (typically at least 100) of individual coated (or "microencapsulated") units contained in the formulation in such a form that the individual units will be made available from the formulation upon disintegration of the formulation in the stomach of animals, including humans, who have ingested the formulation. Typically, the multiple-units formulation may be a capsule which disintegrates in the stomach to make available a multiplicity of individual coated units contained in the capsule, or a tablet which disintegrates in the stomach to make available a multiplicity of coated units originally combined in the tablet.

Drug release from a controlled release dosage form is generally controlled either by *diffusion* through a coating or by *erosion* of a coating by a process dependent on, e.g., enzymes or pH. The importance of a pH independent diffusion with respect to obtaining a reproducible rate of availability and to minimizing intra- and intersubject variations

is known (GB Patent No. 1 468 172 and Bechgaard & Baggesen, 1980). It is also known that controlled drug release *in vivo* can be achieved through an erodable process by enteric coating of a multiple-units dosage form (Green, 1966; McDonald *et al.*, 1977; Bogentoft *et al.*, 1978).

Both above-mentioned types of controlled release multiple-units formulation techniques aim at a controlled release of active substance in a predetermined pattern to reduce and delay the peak plasma concentration without affecting the extent of drug availability. Due to a lower peak plasma concentration, the frequency of undesirable side-effects may be reduced, and due to the delay in the time to obtain the peak plasma concentration and the extension of the time at the therapeutically active plasma level, the dosage frequency may be reduced to daily dosage only twice or once, in order to improve patient compliance.

A further advantage of the controlled release multiple-units dosage form is that high local concentrations of the active substance in the gastrointestinal system is avoided, due to the units being distributed freely throughout the gastrointestinal tract, independent of gastric emptying. If the mucosa of the stomach is more sensitive to the active substance than the intestinal mucosa, controlled release formulations avoiding release of active substance in the gastric area will be preferred; formulations of this type are controlled release multiple-units formulations in which the coatings are substantially resistant to gastric conditions.

DISCLOSURE OF INVENTION

The present invention relates to new developments in controlled release multiple-units formulations where the individual units are coated with an erodable coating.

According to the invention, active substances are incorporated in pharmaceutical oral controlled release multiple-units formulations in which individual units comprise cross-sectionally substantially homo-

geneous cores containing particles of an active substance, the cores being coated with a coating which is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the small intestine.

The individual units of the multiple-units formulations according to the invention will normally be pellets (coated cores) in which the core is constituted by a combination of active substance and excipients. A type of core which is widely used in the known art (*vide*, e.g., Eur. Patent Application No. 79 850 110) is a substantially spherical particle of a size of about 0.5 - 1 mm consisting of excipient(s) with active substance applied to its surface. Typical cores of this type are the so-called "non-pareil" cores where the excipients are in the form of spherical particles of saccharose. It is also known, e.g., from GB Patent Specification No. 1 468 172, to prepare cores which are cross-sectionally substantially homogeneous, but these known cross-sectionally substantially homogeneous cores were coated with a diffusion coating. It is believed that it has not previously been suggested to combine cores which are cross-sectionally substantially homogeneous with an erodable coating. In the present context, the term "cores which are cross-sectionally substantially homogeneous" designates cores in which the active substance is not confined to an exterior layer on the core body, in other words normally cores which, through the cross-section of the core body, contain substantially the same type of composition comprising microparticles containing an active substance, in contrast to the non-pareil type of cores which each consist of an excipient body with active substance applied to its surface, and in contrast to coated crystal units which are substantially monolithic crystals. From this definition, it will be understood that the cores which are cross-sectionally substantially homogeneous will normally consist of a mixture of active substance with excipient(s), (and in spite of the term "homogeneous", this mixture will not necessarily be qualitatively or quantitatively homogeneous through the cross-section of the particle but may show, e.g., a concentration gradient of one or more of its constituents) or they may consist substantially solely of active substance in a non-monolithic form, e.g. as a sintered mass of crystalline or amorphous particles of active

substance. In the following specification and claims, such cores which are cross-sectionally substantially homogeneous will, for the sake of brevity, often simply be designated "cores".

The erodable coatings used in the formulations of the present invention are coatings which are substantially resistant under gastric conditions but are eroded during the passage of the unit through the small intestine. Erodable coatings may be coatings which are eroded by a process dependent on, e.g., enzymes present in the segment of the intestine where the erosion is desired, including enzymes generated by the animal, including the human, to whom the unit is administered and enzymes produced by bacteria, or bacterial fermentation of the erodable coating. As has been explained above, erodable coatings are distinguished from diffusion coatings which are substantially insoluble and non-erodable in gastrointestinal fluids, but are permeable, by diffusion, to gastrointestinal fluids and dissolved active substance. (For the sake of completeness, however, it should be noted that although the quantitatively predominant contribution to the absorption from erodably coated units is the phase following the erosion of the coating it cannot be precluded that a certain amount of active substance will be released through the uneroded coating by diffusion).

An important class of erodable coatings for use in the formulations according to the present invention are the so-called enteric coatings which are coatings that are substantially insoluble under the pH conditions prevailing in the stomach but are soluble at a pH prevailing in the small intestine, typically a pH of above 4.5.

DETAILED DESCRIPTION OF INVENTION

Cores

According to the invention, the cores are cross-sectionally substantially homogeneous cores. The combination of cross-sectionally substantially homogeneous cores with a coating which is substantially

resistant to gastric conditions but is erodable under the conditions prevailing in the small intestine offers several advantages compared to the known art erodably coated cores.

Firstly, it is easy to produce cross-sectionally substantially homogeneous cores reproducibly on a large scale, for instance by means of automatic equipment because the components therefor are normally simply mixed in the prescribed proportions, which means that inter-core variation in composition, e.g., concentration of active substance, can be kept within narrow limits. Secondly, the concentration of active substance in the core can be varied within very wide limits (generally between 10 - 90% by weight), which renders it possible to optimize the concentration of active substance in the single core in order to minimize capsule sizes for a given dosage strength and thereby optimize patient compliance. Thirdly, the size of the cores may be easily adjusted as desired, to improve the distribution pattern of the units throughout the gastrointestinal tract; this forms a contrast to the non-pareil technique where the size variation is limited by the available standard sizes. Fourthly, the composition of the cores may be optimized with respect to the extent of drug availability, i.e., to enhance the release of the active substance in the small intestine, after erosion of the coating.

Thus, it is possible to employ special measures to enhance the absorption of the active substances by enhancing the disintegration of the cores and the dissolution of the active substance. One such special measure according to the invention is to provide the active substance in the cores in the form of particles of a size of about 1 - 10 µm, in particular about 2 - 5 µm, in admixture with components enhancing the disintegration of the cores and the dispersion of the active substance in intestinal fluids.

The cores are typically made by granulating these particles together with excipients, including bulk agents such as carbohydrates and derivatives thereof such as starch and starch derivatives, including microcrystalline cellulose, binders such as cellulose derivatives, including methylcellulose or hydroxypropylmethylcellulose, polyethy-

lene glycol, polyvinylpyrrolidone, agar, or gelatin, for instance by treatment in a high speed mixer (to directly obtain compact-shaped cores), or by treatment in a planet mixer with subsequent extrusion of the mixture into strings of a predetermined diameter approaching the desired final cross-sectional dimension of the cores and treatment of the strings in a marumerizer or similar equipment to obtain compact-shaped cores. The diameter of the cores is normally adapted so that the diameter of the coated core is about 0.4 - 1.2 mm, in particular about 0.5 - 1.0 mm, especially about 0.5 - 0.8 mm, such as 0.5 - 0.7 mm. A preferred diameter of the coated cores is about 0.5 - 0.6 mm. By incorporating special ingredients in the mixture, an increased tendency to disintegrate in contact with intestinal fluids may be imparted to the cores. Examples of such materials are solid insoluble materials which will tend to counteract excessive compaction of the content of the cores during their preparation, and/or to introduce slidability between the components in the cores, and/or to geometrically introduce irregular stresses in the cores, and/or to interfere with the packing of the content of the cores to provide voids between the particles containing active substance, such as plate-shaped bodies, e.g., talc, or compact-shaped particles of a particle size of about 20 - 100 µm, in particular about 50 - 75 µm, such as aluminium silicate, zinc oxide, magnesium oxide, titanium dioxide, colloidal silica, or magnesium trisilicate.

According to a particular aspect of the invention, the disintegration of the cores is additionally accelerated when particles of a substance which is readily soluble in intestinal fluids are incorporated in the mixture from which the cores are made. Examples of such substances are sucrose, glucose, mannitol, sorbitol, or lactose.

In particular, it is preferred to accelerate the disintegration of the cores in intestinal fluids by a combination of the two above-mentioned measures that is, by incorporation of both an insoluble and a soluble disintegration-accelerating component. One example of a combination of this type is the combination of talc and sucrose which is illustrated in the Examples.

The possibility of accelerating the disintegration of the cores is especially valuable in connection with active substances which are sparingly soluble and which, therefore, should be exposed to the intestinal fluids as effectively and speedily as possible after erosion of the coating. In order to obtain maximum disintegration, it is preferred to use only a small amount of binder, if any, in the mixture from which the cores are made.

The weight ratio between the active substance(s) and the excipients may vary within wide limits. Generally, the cores may contain 10 - 90% by weight of active substance. When the active substance is a sparingly soluble substance, the amount of disintegration-enhancing components (insoluble and/or soluble) will often be at least 20% by weight, typically at least 40% by weight, calculated on the total mixture.

In accordance with a particular aspect of the invention, the predetermined controlled release of the active substance may be altered by changing the density of the cores, and thus, the time of arrival of the cores in the predetermined section of the intestine may be varied at will. By increasing the density of the cores resulting in increased transit time of the coated cores (Bechgaard & Ladefoged, 1978), a more delayed and longer lasting absorption phase is obtained, that is a longer period during which the absorption of the active substance takes place after the substance has been released by erosion of the coating, thus having become available for absorption.

Examples of excipients which may be used to increase the density of the cores are described in US Patent No. 4 193 985 and include heavy particulate substances such as barium sulphate, titanium oxide, zinc oxides, and iron salts.

Active Substance

The active substance in the formulations according to the invention may be any active substance which is advantageously administered in a controlled release multiple-units formulation to be made available in

the small intestine, in particular medical substances, including, e.g., methyldopa, morphine, naproxene, prazosin, theophyllin, verapamil, amilorid, and disopyramide.

Especially important formulations according to the invention are formulations in which the active substance, apart from being a substance which from a pharmacokinetic and/or clinical point of view, is known or indicated to be advantageously administered in a controlled release multiple-units formulation, is a substance which exerts an irritating effect on the gastric mucosa such as acetylsalicylic acid, indomethacin, and other non-steroid antiinflammatory drugs, and/or is unstable in acidic environment such as erythromycin, iron salts, cardiac glycosides, e.g., digoxin, and L-Dopa, and/or are sparingly soluble.

The pharmaceutical formulation according to the invention is of particular importance in connection with sparingly soluble active substances, as these are difficult to formulate in accordance with known controlled release dosage forms based on the diffusion principle.

In the present context, the term "sparingly soluble substance" designates a substance which requires more than 30 parts by volume of water to dissolve 1 part by weight of the active substance at ambient temperature. Examples of sparingly soluble active substances are found among almost all therapeutic groups, including diuretics, antiepileptics, sedatives, antiarrhytmics, antirheumatics, β-blockers, vasodilators, analgesics, bronchodilators, hormones, oral antidiabetics, antihypertensives, antiinflammatorics, and antidepressives.

Among the sparingly soluble substances, important substances belong to a group which requires more than 1000 parts by volume of water to dissolve 1 part by weight of the active substance at ambient temperature, or even more than 10,000 parts by volume of water.

As examples of sparingly soluble active substances which may be formulated according to this aspect of the invention may be mentioned indomethacin, spironolactone, ibuprofen, furosemide, sulfadiazine,

sulfamerazine, progesterone, reserpine, pyrvinium embonate, mofebutazone, hydrochlorothiazide, tetracycline, tolbutamide, acetaminophen, testosterone, valproic acid, estradiol, acetazolamide, erythromycin, iron salts, hydralazine, carbamazepine, quinidine, and cardiac glycosides, e.g., digoxin.

As examples of substances among the above-mentioned sparingly soluble substances which require more than 1000 parts by volume of water to dissolve 1 part by weight of the substance at ambient temperature may be mentioned spironolactone, ibuprofen, furosemide, hydrochlorothiazide, tolbutamide, and testosterone.

By utilizing the principle of the invention, it is possible to obtain an extent of availability of a sparingly soluble active substance which is equal to or better than the extent of availability of plain formulations and to reduce and delay the peak plasma concentration compared to plain formulations. This is achieved by utilizing (i) the fact that the units are freely distributed throughout the gastrointestinal tract independently of gastric emptying, as the units are small enough to pass the pylorus even when the sphincter is closed, and (ii) the fact that there is a significant physiological variation along the length of the gastrointestinal tract, including variation in pH and qualitative and quantitative composition of enzymes and microflora. In the stomach, the pH range is wide, viz. pH 1 - 6, primarily due to an increase in pH after the intake of food, while the pH in the small intestine ranges from 5 to 8. The variation in the physiological environment along the length of the small intestine may be utilized by adapting the erodable coating to be eroded in a desired segment of the small intestine. The above-mentioned measures to accelerate the disintegration of the cores is preferably used in combination with special techniques for accelerating the dissolution of the active substance which are explained below in connection with the discussion of the particles containing an active substance.

Particles Containing an Active Substance

The active substance is normally present in the cores in the form of particles of a size in the range from of about 1 to about 75 µm. Normally, the particles are of the conventional sizes in which the particular active substances are available. While active substances which are readily soluble may be available in any size within the range stated above, sparingly soluble substances are typically available as ground materials having particle sizes in the range of about 1 - 10 µm, and this range, in particular the range of about 2 - 5 µm, is normally suitable for sparingly soluble active substances for incorporation in the cores of the present invention.

According to a particularly important embodiment of the invention, active substances which are sparingly soluble are incorporated in the cores in the form of particles in which they are intimately admixed with a substance which is readily dissolved in intestinal fluids and which, therefore, accelerates the dispersion of the active substance. Such an intimate admixture may be obtained, e.g., by co-comminuting the active substance together with the dispersion-accelearting substance, both substances preferably being in solid form during the comminution. The co-comminution may be performed by subjecting a mixture of particles of the active substance with particles of the dispersion-accelerating substance to grinding, in particular high shear grinding, e.g. in a pinned disc mill or a jet mill or other equipment exerting similar stress. The resulting intimate mixture will be in the form of particles in the range of 1 - 10 µm, in particular 2 - 5 µm, in which the active substance and the dispersion-accelerating substance are intimately combined with each other by conglomeration and/or adsorption. The particles in which a sparingly soluble active substance is combined with a dispersion-accelerating substance show an accelerated dissolution of the active substance, which is believed to be due to the fact that the dispersion-accelerating substance incorporated in the particles accelerates the dispersion of the active substance which is thereby more efficiently exposed to the intestinal fluids.

The dispersion-accelerating substance which is incorporated in the particles containing active substance may, in principle, be any pharmaceutially acceptable excipient which is readily soluble in intestinal fluids. Examples of such substances are sucrose, glucose, mannitol, sorbitol or lactose. Especially effective dispersion-accelerating substances are surface-active substances such as detergents, in particular anionic or non-ionic detergents, for instance sodium salts of fatty alcohol sulphates, preferably sodium laurylsulphate, sulfosuccinates, partial fatty acid esters of sorbitans such as sorbitanmonooleate (SPAN®), partial fatty acid esters of polyhydroxyethylene sorbitans such as polyethylene glycolsorbitan monooleate (Tween® 80), or polyhydroxyethylene fatty alcohol ether such as polyhydroxyethylene (23) lauryl ether (BRIJ® 35).

The amount of dispersion-accelerating substance which is incorporated in the particles containing active substance is normally less than 100%, calculated on the active substance, typically at the most 70%, calculated on the active substance. Thus, for instance, when the readily soluble substance is sucrose or another dispersion-accelerating carbohydrate, it is normally co-comminuted with the active substance in an amount of about 40 - 60% by weight, calculated on the active substance. When the dispersion-enhancing substance is a surface-active substance such as a detergent, it is preferably co-comminuted with the active substance in an amount of at the most 10% by weight, preferably about 5% by weight, calculated on the active susbstance.

Coating

The erodable coating applied to the cores according to the invention is preferably an enteric coating which is applied from a solution and/or suspension in an organic solvent and/or water. The application of the coating is typically performed in a fluidized bed or by pan coating.

Examples of enteric coating materials which may be used for the purpose of the present invention are coatings selected from the group consisting of acrylic polymers and copolymers, e.g. a polymerisate of methacrylic acid and methacrylic acid methyl ester such as Eudragit® S 12,5, Eudragit® S 12,5 P (which corresponds to Eudragit® S 12,5 but contains 1.25% of dibutylphthalate), Eudragit® L 30 D or Eudragit® L 12,5, shellac, cellulose acetate esters such as mixed partial esters of cellulose-containing phthalate groups, acetyl groups and free acid groups (cellulose acetate phthalate), polyvinyl acetate esters such as polyvinyl acetate phthalate, hydroxypropylmethyl cellulose esters such as hydroxypropylmethylcellulose phthalate, or alkyleneglycolether esters of copolymers such as partial ethyleneglycol monomethylether ester of ethylacrylate-maleic anhydride copolymer, propyleneglycol monomethylether ester of ethylacrylate-maleic anhydride copolymer, dipropyleneglycol monomethylether ester of ethylacrylate-maleic anhydride copolymer or diethyleneglycol monomethylether ester of methylacrylate-maleic anhydride copolymer, N-butylacrylate-maleic anhydride copolymer, isobutylacrylate-maleic anhydride copolymer or ethylacrylate-maleic anhydride copolymer.

The coating material may be admixed with various excipients such as plasticizers, inert fillers, e.g. talc, pigments, in a manner known *per se*.

The type and amount of enteric coating applied is adapted so as to obtain resistance to gastric environments and release in the desired segment of the small intestine. Normally, the amount of the coating will be about 2 - 25% by weight, calculated as dry matter on the total weight of the cores, typically about 4 - 12% by weight.

In accordance with one aspect of the present invention, the coating is so selected that it will preferably be eroded in the distal part of the small intestine. An example of such a coating is an enteric coating which is substantially insoluble at a pH below 7.

In the present context, the term "an enteric coating which is substantially insoluble at a pH below 7" designates an enteric coating

which, under the experimental conditions defined under MATERIALS AND METHODS below, releases less than 15% of the active substance contained in the coated core within one hour at pH 6.5.

Preferably, the coating which is substantially insoluble at a pH below 7 will, at the same time, effectively release a high proportion of the active substance, typically more than 90% of the active substance contained in the core, within one hour at pH 7.5.

Preferred materials for enteric coatings which are substantially insoluble at a pH below 7 are polymerisates of methacrylic acid and methacrylic acid methyl ester or mixtures thereof. A specific example of such a coating material is Eudragit® S.

The use of a coating which is selectively or preferentially eroded in the distal part of the small intestine offers several advantages:

Firstly, due to the longer passage of the units through the small intestine to reach the distal section of the small intestine in which the pH is in the range of 7 - 8, the time before the peak plasma concentration is reached is prolonged.

It is known that physiological pH variations in the distal segment of the small intestine are small. Furthermore, pH variations caused by food intake are also low in the distal segment. Due to these very stable pH conditions, controlled release formulations of the invention in which the coating is one that is substantially insoluble at pH below 7 will yield a highly reproducible absorption phase, both within and between subjects and are therefore preferred.

As appears from Example 5, the standard deviations of the bioavailability parameters of a formulation according to the invention where the coating is an enteric coating which is substantially insoluble at a pH below 7 were of the same order of magnitude when the formulation was administered with food or after a fast, respectively. The administration of the coated cores concomitantly with food intake did not influence the extent of availability.

The aspect of the invention comprising controlled release multiple-units formulations in which the coating is an erodable coating which erodesselectively in the distal part of the small intestine, in particular an enteric coating which is substantially insoluble at pH below 7, is of general importance and advantage in connection with any type of units, including units which are not cross-sectionally substantially homogeneous.

Therefore, one aspect of the present invention relates to a pharmaceutical oral controlled release multiple-units formulation in which individual units comprising an active substance are coated with a coating which selectively eroded in the distal part of the small intestine. The coating is preferably an enteric coating which is substantially insoluble at a pH below 7, and especially a coating which will release at least 90% of the active substance within one hour at a pH of 7.5 under the experimental conditions defined under MATERIALS AND METHODS below.

Hence, according to this aspect of the invention, the units may be any type of units used in multiple-units formulations. Interesting units, apart from the cross-sectionally substantially homogeneous cores discussed above, are units of the non-pareil type (including units with a concentration gradient of the active substance along the radius of the core), and crystals. The active substances which are formulated according to this aspect of the invention are typically the same as those mentioned above. The preparation of the units according to this aspect of the invention is performed by coating the desired unit types in the same manner as described above.

BRIEF DESCRIPTION OF DRAWING

Fig. 1 is a graph showing the mean concentrations of indomethacin in plasma after single oral doses of 75 mg in the form of a reference formulation (indicated by filled-in circles) or in the form of Coating A capsules according to the invention (indicated by circles) or Coating B capsules according to the invention (indicated by crosses). The concentrations are the ones stated in Example 4.

Fig. 2 illustrates the mean plasma concentration of indomethacin after single oral doses of 75 mg as Coating B capsules according to the invention after a twelve-hour fast (indicated by circles) or within 15 min of ingestion of food (indicated by filled-in circles). The concentrations are the ones stated in Example 5.

The invention is illustrated in greater detail in the following experimental section.

MATERIALS AND METHODS

In the examples, the following materials were used:

Indomethacin:	(2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid); BP 80.
Sodium laurylsulphate:	Ph Eur
Microcrystalline cellulose:	BPC 79.
Sucrose powder:	Ph Eur
Talc:	Ph Eur
Purified water:	Ph Eur
Eudragit® S 12,5:	An anionic polymerisate of methacrylic acid and methacrylic acid methyl ester having a dry matter content of 12.5%, a density D^{20} of 0.84, a viscosity at 20°C of 100 cP; supplied by Röhm Pharma GmbH, Darmstadt, Germany.
Eudragit® L 12,5:	An anionic polymerisate of methacrylic acid and methacrylic acid methyl ester having a dry matter content of 12.5%, a density of D^{20} of 0.84, and a viscosity at 20°C of 75 cP; supplied by Röhm Pharma GmbH, Darmstadt, Germany.

Eudragit® L 30 D:	An anionic polymerisate of methacrylic acid and methacrylic acid methyl ester having a dry matter content of 30% as an aqueous dispersion, supplied by Röhm Pharma GmbH, Darmstadt, Germany.
Acetyltributylcitrate:	Citroflex® A-4; supplied by Pfizer A/S, Copenhagen, Denmark.
Isopropanol:	BP 80.
Polyvinylpyrrolidone:	BP 80 Add 81.
Furosemide:	(4-Chloro-N-furfuryl-5-sulfamoylantranilic acid) BP 80.
Acetylsalicylic acid:	Ph Eur
Triacetin:	(1,2,3-propanetrioltriacetate) USP XX.

Determination of *in vitro* dissolution of pellets or cores:

In vitro dissolution rates were determined according to Baggesen *et al* (1981). The rotation speed was 30 ± 1 r.p.m. and the dissolution medium was 250 ml of 0.1 *M* hydrochloric acid (pH 1.2) or citrate buffer (0.05 *M*, pH 4.5 or 0.02 *M*, pH 6.5) or phosphate buffer (0.05 *M*, pH 7.5), maintained at 37 ± 0.1°C. Release of active substance into the dissolution medium was determined by measuring the absorbance spectrophometrically at 320 nm (indomethacin), 271 nm (furosemide) or 278 nm (the isosbestic point of acetylsalicylic acid/salicylic acid).

EXAMPLE 1

Preparation of Indomethacin-Containing Cores to be Coated with an Enteric Coating

Cores (containing 24% of talc) were prepared from 2.9 kg indomethacin, 0.2 kg sodium laurylsulphate, 0.5 kg microcrystalline cellulose, 4.0 kg sucrose powder and 2.4 kg talc.

The indomethacin and the sodium laurylsulphate were co-comminuted by passage through a grinder using a 0.5 mm sieve.

The ground mixture was mixed with the microcrystalline cellulose, the sucrose and the talc in a planet mixer.

10 kg of the resulting mixture were moistened with 0.8 kg purified water and were mixed in a planet mixer until the mixture was granular.

The moist mixture was extruded through a 0.5 mm sieve. The first kgs of extrudate passing the sieve were powdery and were reextruded. The resulting extrudate were strings breaking off in lengths of 10 - 30 cm.

2 kg of the extruded strings were formed into compact-shaped cores in a marumerizer, and the resulting compact-shaped cores were dried in a fluidized bed dryer and then sieved through a separator, the upper sieve being 0.71 mm, and the bottom sieve 0.46 mm.

In a similar manner as described above, cores (containing 10% of talc) were prepared from 2.9 kg indomethacin, 0.2 kg sodium laurylsulphate, 1.0 kg microcrystalline cellulose, 4.9 kg saccharose powder, and 1.0 kg talc.

The release of the indomethacin was measured, at pH 7.5, as described under MATERIALS AND METHODS, for the cores containing 24% of talc and 10% of talc, respectively. The amount of indomethacin released at pH 7.5 after 10 minutes appears from Table I.

TABLE I

Percentage of indomethacin released at pH = 7.5 after 10 min
(n = 2)

Cores with 24% of talc	98.4%
Cores with 10% of talc	60.0%

It appears from Table I that the increase of the talc content from 10% to 24% results in an increase of the release of indomethacin to practically quantitative release within 10 minutes.

Coating of Cores with Enteric Coating

An enteric coating suspension was prepared by homogenizing 9.0 kg Eudragit® S 12,5 together with 0.135 kg acetyltributylcitrate, 0.9 kg talc and 7.965 kg isopropanol.

10 kg of the above-described cores containing 24% of talc were coated with 4.167 kg of this coating suspension in a fluidized bed, and the resulting pellets were covered with talc.

For the preparation of a pharmaceutical dosage form, more than 1000 of these pellets were filled into a capsule No. 1. Each capsule contained 75 mg indomethacin.

EXAMPLE 2

The Effect of Dispersion-Accelerating Agents with Respect to Improving the Dissolution of the Active Substance

In a similar manner as described in Example 1, (but without co-comminution of the indomethacin with any dispersion-accelerating agent), cores were prepared from 3.2 kg indomethacin, 1.0 kg microcrystalline cellulose, 5.7 kg sucrose powder and 0.1 kg polyvinylpyrrolidone. These cores are designated cores, type 0.

Another portion of cores, designated cores, type SACH, was prepared from the same ingredients in a similar manner, except that in this case the indomethacin and the sucrose powder were co-comminuted by passage through a grinder using a 0.5 mm sieve.

In the same manner as described in Example 1, cores were made from 3.2 kg indomethacin, 0.2 kg sodium laurylsulphate, 1.0 kg microcrystalline cellulose, 5.5 kg sucrose powder and 0.1 kg polyvinylpyrrolidone. These cores are designated cores, type NaLS.

The release of the indomethacin was measured, at pH 7.5, as described under MATERIALS AND METHODS for these 3 types of cores.

The amount of indomethacin released at pH 7.5 after 10 minutes appears from Table II.

TABLE II

Percentage of Indomethacin released at pH = 7.5 after 10 min (n = 2)

Cores, type 0	71.0%
Cores, type SACH	92.8%
Cores, type NaLS	97.1%

It appears from Table II that the release of indomethacin is considerably increased when a dispersion-accelerating agent is co-comminuted with the indomethacin, and that the detergent type of dispersion-accelerating agent results in the fastest release.

EXAMPLE 3

The Influence of Coatings Soluble at Different pH on the Dissolution of Indomethacin

An enteric coating suspension was prepared as described in Example 1 from 2.08 kg Eudragit® L12.5, 2.08 kg Eudragit® S12.5, 0.0625 kg acetyltributylcitrate, 0.417 kg talc and 3.69 kg isopropanol.

This coating, which is soluble at pH above 6.5, was called Coating A.

An enteric coating suspension was prepared as described in Example 1 from 4.16 kg Eudragit® S12.5, 0.0625 kg acetyltributylcitrate, 0.417 kg talc and 3.69 kg isopropanol.

This coating, which is soluble at pH above 7.0, was called Coating B.

Cores containing sodium laurylsulphate and 24% of talc, prepared as described in Example 1, were coated with 10% of Coating A or 10% of Coating B (% dry matter of coating, calculated on the weight of the core). The dissolution of indomethacin from the resulting two types of pellets was determined as described under MATERIALS AND METHODS. The results are stated in Table III.

TABLE III

Percentage of indomethacin released at pH 6.5 and pH 7.5
(n = 3)

	pH = 6.5			pH = 7.5
	10 m	30 m	60 m	60 m
Coating A	17.4	64.0	76.5	98.6
Coating B	6.5	9.0	9.8	100.7

It appears from Table III that cores coated with Coating A and Coating B quantitatively released the indomethacin at pH 7.5 within 60 minutes and that cores coated with Coating B only released about 10% of indomethacin after 1 h at pH 6.5. The possibility of adjusting the enteric coating is very important because it makes it possible to tailor formulations to be disintegrated in a predetermined segment of the small intestine.

EXAMPLE 4

Bioavailability of Indomethacin from two Multiple-units Controlled Release Formulations

Drug formulations:

The two types of indomethacin-containing pellets prepared in Example 3 (designated Coating A and Coating B, respectively) were formulated into hard gelatin capsules designated Coating A and Coating B capsules, respectively. Each capsule of each formulation contained 75 mg indomethacin. Instant release capsules of indomethacin (Indocid®, Merck, Sharp and Dohme Ltd.) were used as the reference formulation. Each capsule of the reference formulation contained 25 mg indomethacin. Indomethacin was almost completely released from this capsule formulation during 10 minutes at pH 6.5.

Drug administration:

Eight healthy normal adult male subjects of an age range of 21-24 years and a body weight range of 60-80 kg were selected for this study.

Each subject fasted for 12 hours before drug administration and remained fasting for 4 hours afterwards. Administration was conducted in a three-way complete crossover with one week between dosing, in which each subject received orally one Coating A or B capsule or three capsules of the reference formulation (75 mg total dose) together with 100 ml water. Blood samples (10 ml) were withdrawn before dosing and at intervals during the following 24 hours.

Measurement of indomethacin in plasma:

Concentrations of indomethacin in plasma were measured using a high performance liquid chromatographic (HPLC) method. Plasma (200 µl for concentrations between 0.1 µg/ml and 4 µg/ml or 100 µl for concentrations above 4 µg/ml containing 1 µg mefenamic acid as an internal standard) was mixed with phosphate buffer (1 ml, 1 *M*, pH 5.0),

and extracted with freshly distilled diethyl ether (5 ml) for 10 minutes on a rotary mixer. The phases were separated by centrifugation and the organic phase was removed and evaporated to dryness under nitrogen at 37°C. The residue was washed to the bottom of the tube with a small amount of ether which was then evaporated to dryness.

The drug residues were dissolved in methanol (50 µl), portions (20 µl) of which were injected into the HPLC system which consisted of an automatic injector and pump (Waters Associates Ltd., U.K.), fitted with a variable wavelength ultra-violet monitor (Pye Unicam Ltd., U.K.) operated at 260 nm (λmax for indomethacin in methanol). The stainless steel column (30 cm x 0.4 cm i.d.) was prepacked with µ Bondapak C_{18} (mean particle size 10 µm, Waters Associates Ltd.) and a stainless steel precolumn (7 cm x 0.2 cm i.d.) drypacked with pellicular Co:Pell® ODS (particular size 25 - 37µm, Whatman Ltd., UK) was installed to protect the analytical column. Chromatography was performed in reversed-phase mode with a mobile phase of acetonitrile (62%, v/v) in phosphate buffer (0.1 *M*, pH 4.0) at a flow rate of 2.5 ml/min. Indomethacin and the internal standard (mefenamic acid) were eluted with retention times of 2.7 and 3.6 minutes respectively.

Linear calibration curves of peak area ratio of indomethacin to internal standard were constructed by analysis of plasma containing these compounds over the concentration range 0.1 µg/l - 4 µg/l. The standard error of taking the calibration line as a measure of indomethacin concentration over this range was 0.12 µg/ml. The recovery of the internal standard at the level added of 5 µg/ml was 100% ± 4 S.D. (n = 5), and the mean recovery of indomethacin over the concentration range 0.5 µg/l - 4 µg/l was 103% ± 3 S.D. (n = 5). No peaks were present on chromatograms of extracts of predose plasma in the position of the internal standard, but in some samples of predose plasma, interfering material was present at the position of indomethacin and equivalent to a maximum of 0.1 µg/ml. The limit of detection was therefore arbitrarily set at 0.1 µg/ml. The precision of measurement was assessed by the coefficients of variation of the means of replicate measurements (n = 6) of ± 17% at 0.1 µg/ml, ± 2% at 2 µg/ml

and ± 4% at 4µg/ml. Known metabolites of indomethacin did not interfere with the measurement of the unchanged drug above a limit of 0.1 µg/ml.

Data processing:

Areas to 24 h (AUC) under the plasma concentration-time curves were calculated by the trapezoidal rule. Since plasma drug levels at 24 h after dosing were close to the limit of detection, these areas were considered to be equivalent to areas to infinite time. Since drug administration was unbalanced with respect to the dosing sessions, AUCs, peak plasma levels and their times of occurrence, times to reach a plasma level of 1.0 µg/ml were subjected to analysis of variance by regression techniques. Overall formulation-related effects were examined by the F-test and formulation means were tested pair-wise by the method of least significant differences (Snedecor & Cochran, 1967).

Results:

Peaks of mean plasma concentrations of indomethacin of 4.9 µg/ml, 3.0 µg/ml and 2.3 µg/ml occurred after single oral doses of 75 mg of the reference formulation and the Coating A and B capsule formulations respectively and these peaks of mean levels occurred at 1 h, 2 h and 3 h respectively, vide Fig. 1.

Indomethacin was more slowly absorbed from both Coating A and B capsules than from the reference capsules, and was more slowly absorbed from the Coating B capsules than it was from the Coating A capsules.

The bioavailability parameters appear in Table IV. The differences between formulations within these parameters are highly significant except for the AUC.

TABLE IV

Mean values of bioavailability parameters of indomethacin after administration of the reference and coating A and B capsules, respectively. Standard deviations are in parentheses

	Reference	Coating A	Coating B
Area (µg h/ml)	12.2 (4.0)	13.7 (4.3)	11.8 (2.4)
Peak plasma concentration (µg/ml)	5.5 (1.2)	3.8 (1.2)	2.9 (0.8)
Time of peak concentration (h)	1.0 (0.3)	2.1 (0.6)	3.5 (0.9)
Time to 1 µg/ml[a] (h)	0.4 (0.2)	1.2 (0.3)	2.4 (0.7)

[a] Time after dosing required to reach a plasma concentration of 1 µg/ml, by interpolation.

These data imply a considerable slower absorption rate after administration of the Coating B capsules compared with Coating A capsules and the reference formulations. The extent of bioavailability, however, was similar after administration of each preparation.

Discussion:

Formulation of indomethacin as multiple-units controlled-release capsules comprising enteric-coated pellets of different sensitivity to an alkaline environment did not affect the extent of drug bioavailability, and drug absorption was slower after administration of these pellets when compared with the standard reference formulation. Rates of absorption were in the order: reference formulation > Coating A capsules > Coating B capsules (Table IV); thus it was demonstrated

that these absorption rates are ranked in order of their observed dissolution rates *in vitro* (Table III).

The present formulation technique takes into account the transit time and distribution of the pellets throughout the gastrointestinal tract (Bechgaard & Ladefoged, 1978) and the characteristic of a strictly alkaline-dependent erosion of the coating of pellets. The data confirm that the drug release from these pellets *in vivo* was dependent on an alkaline pH and that dissolution probably occurred in the distal part of the gastrointestinal tract, where the pH is relatively high (pH 6.5 - 7.5) and less variable than that in the proximal small intestine, which factor is more important in the non-fasting state. This finding is further supported by the low observed standard deviations of the bioavailability parameters after administration of the Coating A and B capsules (Table IV). These standard deviations were of the same order of magnitude as those after administration of the standard reference formulation. Thus the present multiple-units controlled release formulations represent a reliable and reproducible source of indomethacin.

EXAMPLE 5

The Effect of Food on the Bioavailability of Indomethacin from a Multiple-units Controlled Release Formulation

Drug formulation:

Coating B capsules each containing 75 mg indomethacin, as described in Example 4.

Drug administration:

Nine healthy adult male subjects of an age range of 22 - 36 years and a body weight range of 63 - 70 kg, were selected for this study.

Administration was conducted as a complete crossover with one week between doses, in which each subject received a single oral dose of one capsule (75 mg) together with 100 ml water, once after a 12-hour fast, and once after they had received a breakfast consisting of cereal, egg, bacon and sausage, one slice of toast and one cup of coffee, within 15 minutes of drug administration. Blood samples were withdrawn before dosing, and at intervals during the following 24 hours.

Measurement of indomethacin in plasma:

Concentrations of indomethacin in plasma were measured by a high performance liquid chromatographic method, as described in Example 4.

Data processing:

Areas to 24 h (AUC) under the plasma concentration-time curves were calculated by the trapezoidal rule. Peak plasma concentrations and times of their occurence, AUC, and times to reach a plasma concentrations of 1 µg/ml were subjected to analyses of variance for cross-over designs (Snedecor & Cochran, 1967), with subjects, dosing sessions, treatments and residual as factors in the analysis. The statistical significance of treatment differences was tested by the method of least significant differences.

Results:

A peak of mean concentrations of indomethacin in plasma of 1.9 µg/ml occurred at 5 hours after administration of 75 mg after a 12 h fast, and indomethacin was present (0.2 µg/ml) in plasma withdrawn 24 h after dosing. When 75 mg was administered within 15 min of ingestion of a substantial breakfast, the peak of mean plasma concentrations of indomethacin (1.8 µg/ml) occurred at 6 h after which mean plasma indomethacin concentrations declined to 0.4 µg/ml at 24 hours, *vide* Fig. 2.

Two peak levels of indomethacin concentrations were present in the plasma of most subjects upon administration after a period of fasting as well as together with food, but this effect was more noticeable when the doses were administered together with food.

Indomethacin is thought to undergo enterohepatic recirculation in humans, and the secondary peak plasma concentrations may have been an expression of this recirculation.

The overall major peak plasma concentrations and AUC were not significantly different ($P>0.05$) after administration of Coating B capsules either after a twelve-hour fast or together with food (Table V).

TABLE V

Mean bioavailability parameters of indomethacin. Standard deviations in parentheses

(n = 9)

	Fasting		With food ingestion		
Area (µg.h/ml)	13.8	(3.8)	12.5	(2.6)	NS
Peak level (ng/ml):					
First	2.7	(0.8)	2.2	(1.0)	NS
Second	0.5[a]	(0.2)	1.1[b]	(0.8)	NS
Time of peak level (h):					
First	4.2	(1.4)	6.4	(2.2)	P<0.05
Second	12.7	(1.0)	14.4	(6.8)	NS
Time (h) to reach 1 µg/ml[a]	3.0	(1.3)	5.5	(2.6)	P<0.05

[a] Secondary peak concentrations were present in the plasma of 6 subjects

[b] Secondary peak concentrations were present in the plasma of 7 subjects

Significance levels refer to treatment differences from the analysis of variance. NS = not significant ($P>0.05$)

The time of occurrence of the first peak plasma level after administration together with food (6.4 h) was later than, and significantly different from ($P<0.05$), that after administration after a twelve-hour fast (4.2 h), but corresponding times of occurrence of the second peak levels were not statistically significantly different. The time required to reach a plasma concentration of 1 µg/ml after administration together with food (5.5 h) was longer than, and significantly different from ($P<0.05$), that after administration after fasting (3.0 h), as seen from Table V.

Discussion:

Administration of Coating B capsules with food did not affect the extent of drug bioavailability, but the presence of food decreased the rate of bioavailability as indicated by the later, and statistically significantly different, time of occurrence of the first peak plasma concentration and the time to achieve a plasma concentration of 1 µg/ml. The phenomenon of the double peak concentration was also exaggerated after administration with food. Apparently, the extent to which a concomitant meal influences the bioavailability of indomethacin from Coating B capsules is equal to that from a plain indomethacin capsule. It should be emphasized that the observed standard deviations of the bioavailability parameters were of the same order of magnitude when the drug was administered together with food or after a fast, as seen from Table V. Thus, the controlled release multiple-units formulation according to the invention represents a reliable and reproducible source of indomethacin when administered together with food.

EXAMPLE 6

Preparation of Furosemide-Containing Cores to be Coated with an Enteric Coating

Cores were prepared from 40 g of furosemide, 10 g of sucrose powder, 10 g of microcrystalline cellulose, 25 g of sucrose powder and 15 g of talc.

The furosemide and 10 g of the sucrose were passed through a grinder using a 0.5 mm sieve.

The powder was mixed with the microcrystalline cellulose, the remainder of the sucrose and the talc in a planet mixer.

100 g of the resulting mixture was moistened with 12 g purified water and was mixed until the mixture was granular.

The moist mixture was extruded through a 0.5 mm sieve.

The resulting extrudate was formed into compact-shaped cores in a marumerizer, and the cores were dried in a fluidized bed; the dried cores were sieved, the upper sieve being 0.71 mm, and the bottom sieve 0.46 mm.

Coating of Cores with Enteric Coating

An enteric coating suspension (C) was prepared by homogenizing 11.4 g Eudragit® L 30 D together with 0.6 g triacetin and 8 g purified water.

Another enteric coating suspension (D) was prepared by homogenizing 25.0 g Eudragit® S 12.5 together with 0.375 g acetyltributylcitrate, 2.5 g talc and 22.1 g isopropanol.

Portions of each 100 g of the cores obtained above were coated with coating suspension C and D, respectively, in a fluidized bed, and the resulting pellets were covered with talc.

The release of furosemide from the resulting pellets was determined as described under MATERIALS AND METHODS. The results are stated in Table VI.

TABLE VI

Percentage of furosemide released at pH 4.5 and at pH 7.5 (n = 2)

	pH 4.5	pH 7.5
	120 m	30 m
Coating C	16.9	95.4
Coating D	14.3	96.5

It appears from Table VI that the release of furosemide is practically quantitative at pH 7.5, and that the furosemide is released very slowly at pH 4.5.

EXAMPLE 7

Preparation of Enteric Coated Acetylsalicylic Acid Crystals

An enteric coating suspension was prepared by homogenizing 59.4 g Eudragit® S 12.5 together with 0.9 g acetyltributylcitrate, 11.7 g talc and 46.8 g isopropanol.

100 g of acetylsalicylic acid crystals having a size from 0.3 to 0.7 mm were coated with 20% (% dry matter of coating, calculated on crystals) of this enteric coating suspension in a fluidized bed.

The dissolution of acetylsalicylic acid from these coated crystals was determined as described under MATERIALS AND METHODS. The results are stated in Table VII.

TABLE VII

Percentage of acetylsalicylic acid released at pH 1.2, pH 6.5 and pH 7.5
(n = 3)

	pH = 1.2	pH = 6.5	pH = 7.5
	60 m	60 m	60 m
	3.2	5.7	100.0

It appears from Table VII that the release of acetylsalicylic acid is practically quantitative at pH 7.5, and that there is only a very slow release at pH 1.2.

For the preparation of a pharmaceutical dosage form, 500 mg of the coated crystals obtained above were filled into a capsule No. 00.

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Claims:

1. A pharmaceutical oral controlled release multiple-units formulation in which individual units comprise cross-sectionally substantially homogeneous cores containing particles of an active substance, the cores being coated with a coating which is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the small intestine.

2. A formulation according to claim 1 which is a capsule or tablet formulation which disintegrates substantially immediately upon ingestion in the stomach into a multiplicity of individual units which are distributed freely throughout the gastrointestinal tract.

3. A formulation according to claim 1 or 2 in which the cores comprise substantially homogeneous mixtures.

4. A formulation according to any of the preceding claims in which the active substance is a substance which exerts an irritating effect on the gastric mucosa, and/or is unstable in an acidic environment, and/or is sparingly soluble.

5. A formulation according to claim 4 in which the active substance is a substance which requires more than 30 parts by volume of water to dissolve 1 part by weight of the active substance at ambient temperature.

6. A formulation according to claim 5 in which the sparingly soluble active substance is a substance which requires more than 1000 parts by volume of water to dissolve 1 part by weight of the active substance at ambient temperature.

7. A formulation according to any of the preceding claims in which the active substance is present in the cores in the form of particles of a size of about 1 - 10 µm, in particular about 2 - 5 µm, together with components accelerating the disintegration of the cores in intestinal fluids.

8. A formulation according to claim 7 in which the components accelerating the disintegration of the cores in intestinal fluids comprise insoluble bodies, such as plate-shaped bodies, e.g., talc, and/or compact-shaped bodies, such as aluminium silicate, zinc oxide, magnesium oxide, titanium dioxide, colloidal silica or magnesium trisilicate.

9. A formulation according to claim 7 or 8 in which the disintegration-accelerating components comprise particles of a substance which is readily soluble in intestinal fluids such as sucrose, glucose, mannitol, sorbitol or lactose.

10. A formulation according to claim 9 wherein the disintegration-accelerating components comprise a combination of talc and sucrose.

11. A formulation according to any of claims 7 - 10 in which the active substance is present in the form of 1 - 10 µm particles in which it is in intimate admixture with a substance which is readily dissolved in intestinal fluids to disperse the particles.

12. A formulation according to claim 11 wherein particles contain the dispersion-accelerating substance in an amount of at the most 10% by weight, calculated on the active substance.

13. A formulation according to claim 11 or 12 in which the substance which is readily dissolved in intestinal fluids to disperse the particles is a surface-active substance such as an anionic detergent.

14. A formulation according to claim 13 in which the surface-active substance is selected from the group consisting of sodium salts of fatty alcohol sulphates, sulphosuccinates, partial fatty acid esters of sorbitans such as sorbitanmonooleate, partial fatty acid esters of polyhydroxyethylene sorbitans such as polyethylene glycolsorbitan monooleate or polyhydroxyethylene fatty alcohol ether such as polyhydroxyethylene (23) lauryl ether.

15. A formulation according to claim 14 in which the surface-active substance is sodium laurylsulphate.

16. A pharmaceutical formulation according to any of claims 1 - 15 in which the erodable coating is an enteric coating.

17. A formulation according to claim 16 in which the enteric coating is selected from the group consisting of acrylic polymers and copolymers, e.g. a polymerisate of methacrylic acid and methacrylic acid methyl ester, shellac, cellulose acetate esters such as mixed partial esters of cellulose containing phthalate groups, acetyl groups and free acid groups (cellulose acetate phthalate), polyvinyl acetate esters such as polyvinyl acetate phthalate, hydroxypropylmethyl cellulose esters such as hydroxypropylmethylcellulose phthalate, or alkyleneglycolether esters of copolymers such as partial ethyleneglycol monomethylether ester of ethylacrylate-maleic anhydride copolymer, propyleneglycol monomethylether ester of ethylacrylate-maleic anhydride copolymer, dipropyleneglycol monomethylether ester of ethylacrylate-maleic anhydride copolymer or diethyleneglycol monomethylether ester of methylacrylate-maleic anhydride copolymer, N-butylacrylate-maleic anhydride copolymer, isobutylacrylate-maleic anhydride copolymer or ethylacrylate-maleic anhydride copolymer.

18. A formulation according to any of claims 1 - 16 wherein the coating is a coating which erodes selectively in the distal part of small intestine.

19. A formulation according to claim 18 wherein the erodable coating is an enteric coating which is substantially insoluble at a pH below 7.

20. A formulation according to claim 19 in which the enteric coating comprises an acrylic polymer.

21. A formulation according to claim 20 in which the enteric coating comprises an anionic polymerisate of methacrylic acid and methacrylic acid methyl ester or mixtures thereof.

22. A formulation according to claim 21 in which the enteric coating comprises Eudragit® S.

23. A formulation according to any of claims 7 - 22 in which the diameter of each coated core is about 0.4 - 1.2 mm, in particular about 0.5 - 1.0 mm, especially about 0.5 - 0.8 mm, such as 0.5 - 0.7 mm.

24. A formulation according to any of claims 16 - 23 wherein the amount of enteric coating is about 2 - 25% by weight, calculated on the total weight of the multiple-units.

25. A formulation according to claim 24 in which the cores each have a diameter of about 0.5 - 0.6 mm, and the amount of enteric coating applied is about 4 - 12% by weight, calculated on the total weight of the cores.

26. A formulation according to any of the preceding claims in which the active substance is selected from the group consisting of indomethacin, spironolactone, ibuprofen, furosemide, sulfadiazine, sulfamerazine, progesterone, reserpine, pyrvinium embonate, mofebutazone, hydrochlorothiazide, tetracycline, tolbutamide, acetaminophen, testosterone, valproic acid, estradiol, acetazolamide, erythromycin, iron salts, hydralazine, carbamazepine, quinidine, and cardiac glycosides, e.g., digoxin.

27. A formulation according to any of claims 1 - 26 in which the active substance is selected from the group consisting of methyldopa, morphine, naproxene, prazosin, theophyllin, verapamil, amilorid, and disopyramide.

28. A formulation according to any of claims 1 - 26 in which the active substance is selected from the group consisting of acetylsalicylic acid, and other non-steroid antiinflammatory drugs.

29. A formulation according to any of claims 1 - 26 in which the active substance is selected from the group consisting of erythromycin, iron salts, cardiac glycosides, e.g., digoxin, and L-Dopa.

30. A formulation according to any of the preceding claims in the form of a capsule.

31. An individual unit showing the features stated in any of claims 1 - 29.

32. A method for preparing a pharmaceutical oral controlled release multiple-units formulation or units therefor, comprising comminuting an active substance together with a substance which is readily soluble in intestinal fluids to obtain particles containing the active substance intimately admixed with the said substance, combining the resulting particles into cross-sectionally substantially homogeneous cores together with components which accelerate the disintegration of the cores in intestinal fluids, coating the individual cores with an erodable coating, and, if desired, combining a multiplicity of the coated cores into a capsule or tablet formulation.

33. A pharmaceutical oral controlled release multiple-units formulation in which individual units comprising an active substance are coated with a coating which erodes selectively in the distal part of the small intestine.

34. A formulation according to claim 33 in which the coating is an enteric coating which is substantially insoluble at a pH below 7.

35. A formulation according to claim 34 in which the enteric coating is a coating which will release at least 90% of the active substance within one hour at a pH of 7.5 under the experimental conditions defined herein.

36. A formulation according to any of claims 33 - 35 in which the units are cross-sectionally substantially homogeneous cores, or units of the non-pareil type, or crystals.

37. A formulation according to any of claims 33 - 36 in which the enteric coating comprises an acrylic polymer.

38. A formulation according to claim 37 in which the enteric coating comprises an anionic polymerisate of methacrylic acid and methacrylic acid methyl ester or mixtures thereof.

39. A formulation according to claim 21 in which the enteric coating comprises Eudragit® S.

40. A formulation according to any of claims 33- 39 in which the amount of enteric coating is about 2 - 25% by weight, calculated on the total weight of the multiple-units.

41. A formulation according to any of claims 33 - 40 in which the active substance is selected from the group consisting of indomethacin, spironolactone, ibuprofen, furosemide, sulfadiazine, sulfamerazine, progesterone, reserpine, pyrvinium embonate, mofebutazone, hydrochlorothiazide, tetracycline, tolbutamide, acetaminophen, testosterone, valproic acid, estradiol, acetazolamide, erythromycin, iron salts, hydralazine, carbamazepine, quinidine, and cardiac glycosides, e.g., digoxin.

42. A formulation according to any of claims 33 - 40 in which the active substance is selected from the group consisting of methyldopa, morphine, naproxene, prazosin, theophyllin, verapamil, amilorid, and disopyramide.

43. A formulation according to any of claims 33 - 40 in which the active substance is selected from the group consisting of acetylsalicylic acid, and other non-steroid antiinflammatory drugs.

44. A formulation according to any of claims 33 - 40 in which the active substance is selected from the group consisting of erythromycin, iron salts, cardiac glycosides, e.g., digoxin, and L-Dopa.

45. A unit showing the features according to any of claims 33 - 44.

1/2

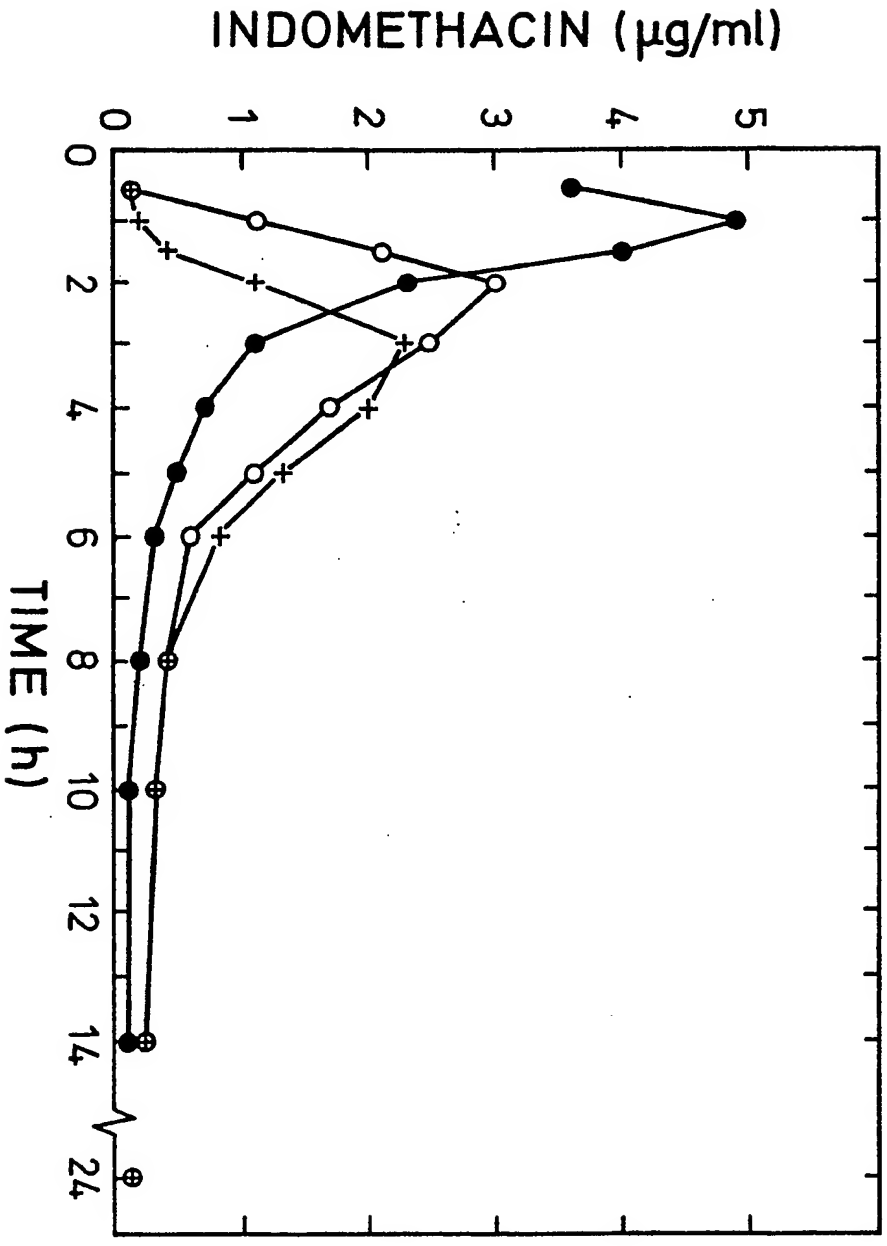

Fig. 1.

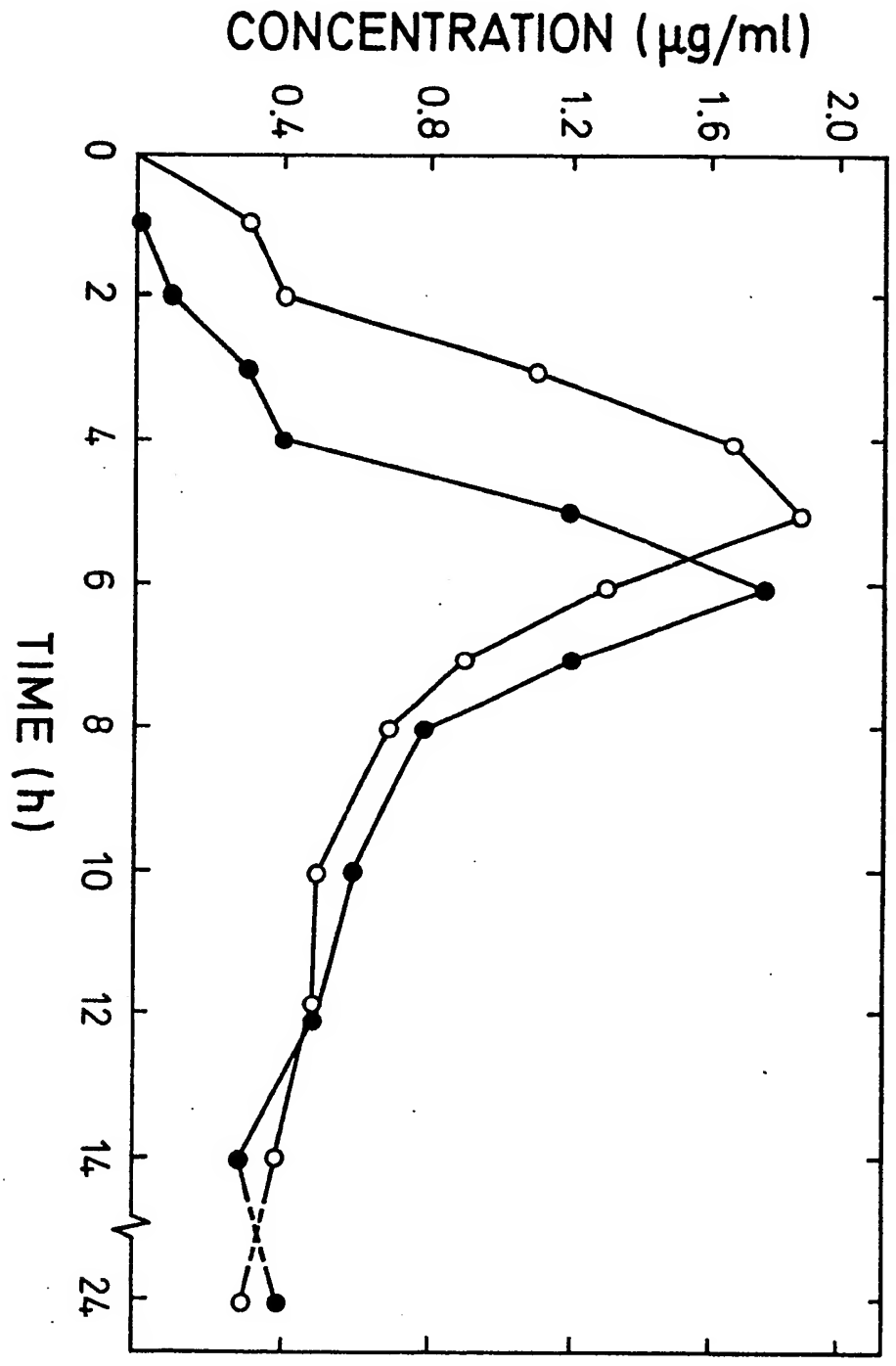

Fig. 2.